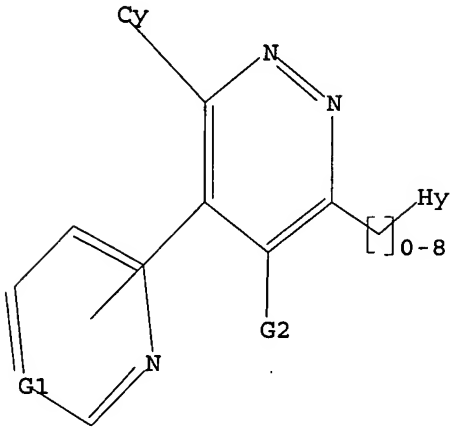
(2)

O,OO-1
N,N1-2

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



G1 C,N
G2 Ak,X,A,NO2,CN,C,O,S,N

Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SEARCH INITIATED 10:30:31 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 2001 TO ITERATE

100.0% PROCESSED 2000 ITERATIONS 0 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 37337 TO 42703
PROJECTED ANSWERS: 0 TO 0

L2 0 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 10:30:48 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 37122 TO ITERATE

100.0% PROCESSED 37122 ITERATIONS 8 ANSWERS
SEARCH TIME: 00.00.01

L3 8 SEA SSS FUL L1

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=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   166.94     167.15

FILE 'CAPLUS' ENTERED AT 10:30:56 ON 21 SEP 2006
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FILE COVERS 1907 - 21 Sep 2006  VOL 145 ISS 13
FILE LAST UPDATED: 20 Sep 2006  (20060920/ED)

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They are available for your review at:

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=> s l3
L4            1 L3

=> d ibib abs hitstr
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OWN WORK

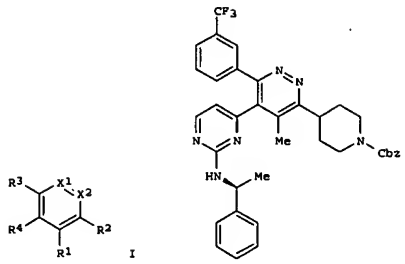
L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:927172 CAPLUS
DOCUMENT NUMBER: 141:395567
TITLE: Preparation of substituted pyridazines and analogs for treatment of TNF-α, IL-1β, IL-6, and/or IL-8 mediated disorders
INVENTOR(S): Dominguez, Celia; Goldberg, Martin H.; Tamayo, Nuria A.
PATENT ASSIGNEE(S): Amgen Inc., USA
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004094379	A2	20041104	WO 2004-US11953	20040415
WO 2004094379	A3	20050331		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004254178	A1	20041216	US 2004-826982	20040415
EP 1628665	A2	20060301	EP 2004-750293	20040415
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				

PRIORITY APPLN. INFO.: US 2003-463697P P 20030416
WO 2004-US11953 W 20040415

OTHER SOURCE(S): MARPAT 141:395567
GI

L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)



I II

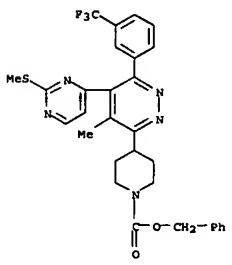
AB Title compds. I [wherein X1, X2 = independently (un)substituted CH, N; with the proviso that at least one of X1 and X2 = N; R1 = (halo)alkyl, CN, NO2, acyl, carboxy, carbamoyl, alkoxy, sulfamoyl, ureido, etc.; R2 = alkyl, Ph, PhCH2, heterocyclyl, etc.; R3, R4 = independently (un)substituted Ph, naphthyl, heterocyclyl; or pharmaceutically acceptable salts thereof] were prepared as TNF-α, IL-1β, IL-6, and/or IL-8 inhibitors. For example, a multi-step synthesis concluding with the reaction of 4-[5-(2-methanesulfonylpyrimidin-4-yl)-4-methyl-6-(3-trifluoromethylphenyl)pyridazin-3-yl]piperidine-1-carboxylic acid benzyl ester and (S)-(-)-1-phenylethylamine gave II. The latter inhibited lipopolysaccharide-activated THP1 cell TNF-α production with IC50 <20 μM. Thus, I and their pharmaceutical compns. are useful for the treatment of inflammation, rheumatoid arthritis, Paget's disease, osteoporosis, multiple myeloma, uveitis, acute or chronic myelogenous leukemia, pancreatic b cell destruction, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, allergic rhinitis, ulcerative colitis, anaphylaxis, contact dermatitis, asthma, muscle degeneration, cachexia, Reiter's syndrome, type I diabetes, type II diabetes, bone resorption diseases, graft vs. host reaction, Alzheimer's disease, stroke, myocardial infarction, ischemia reperfusion injury, atherosclerosis, brain trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, myalgias due to HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses, or herpes zoster infection (no data).

IT 786705-13-3P, 4-[4-Methyl-5-(2-methylsulfanylpyrimidin-4-yl)-6-(3-trifluoromethylphenyl)pyridazin-3-yl]piperidine-1-carboxylic acid benzyl ester 786705-15-5P, 4-[5-(2-Methylsulfonylpyrimidin-4-yl)-4-methyl-6-(3-trifluoromethylphenyl)pyridazin-3-yl]piperidine-1-carboxylic

L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)

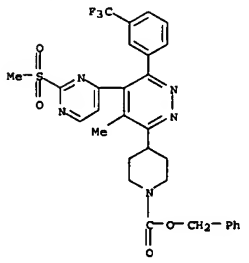
acid benzyl ester 786705-17-7P, 4-[4-Methyl-5-[2-(1-phenylethylamino)pyrimidin-4-yl]-6-(3-trifluoromethylphenyl)pyridazin-3-yl]piperidine-1-carboxylic acid benzyl ester 786705-19-9P, [4-[5-Methyl-6-(piperidin-4-yl)-3-(3-trifluoromethylphenyl)pyridazin-4-yl]pyrimidin-2-yl](1-phenylethyl)amine 786705-21-3P, 2-Hydroxy-1-[4-[4-methyl-5-[2-(1-phenylethylamino)pyrimidin-4-yl]-6-(3-trifluoromethylphenyl)pyridazin-3-yl]piperidin-1-yl]propan-1-one 786705-23-5P, (S)-4-[4-Methyl-5-[2-(1-phenylethylamino)pyrimidin-4-yl]-6-(3-trifluoromethylphenyl)pyridazin-3-yl]piperidine-1-carboxylic acid benzyl ester 786705-25-7P, [4-[5-Methyl-6-(piperidin-4-yl)-3-(3-trifluoromethylphenyl)pyridazin-4-yl]pyrimidin-2-yl]((S)-1-phenylethyl)amine 786705-27-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(TNF and/or IL inhibitor; prepn. of substituted pyridazines and analogs as TNF and IL inhibitors for treatment inflammation, pain, and other disorders)

RN 786705-13-3 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[4-methyl-5-(2-(methylthio)-4-pyrimidinyl]-6-[3-(trifluoromethyl)phenyl]-3-pyridazinyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

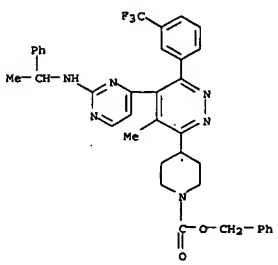


RN 786705-15-5 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[4-methyl-5-[2-(methylsulfonyl)-4-pyrimidinyl]-6-[3-(trifluoromethyl)phenyl]-3-pyridazinyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)

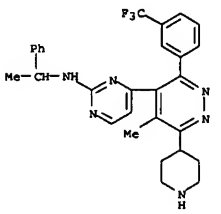


RN 786705-17-7 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[4-methyl-5-[2-[(1-phenylethyl)amino]-4-pyrimidinyl]-6-[3-(trifluoromethyl)phenyl]-3-pyridazinyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

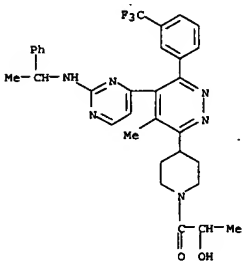


RN 786705-19-9 CAPLUS
CN 2-Pyrimidinamine, 4-[5-methyl-6-(4-piperidinyl)-3-[3-(trifluoromethyl)phenyl]-4-pyridazinyl]-N-(1-phenylethyl)- (9CI) (CA INDEX NAME)

L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)



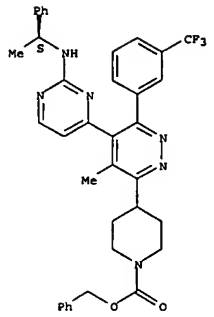
RN 786705-21-3 CAPLUS
CN Piperidine, 1-(2-hydroxy-1-oxopropyl)-4-[4-methyl-5-[2-[(1-phenylethyl)amino]-4-pyrimidinyl]-6-[3-(trifluoromethyl)phenyl]-3-pyridazinyl]- (9CI) (CA INDEX NAME)



RN 786705-23-5 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[4-methyl-5-[2-[[(1S)-1-phenylethyl]amino]-4-pyrimidinyl]-6-[3-(trifluoromethyl)phenyl]-3-pyridazinyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

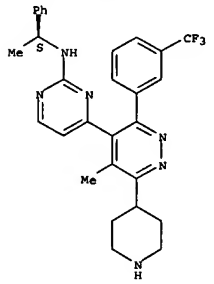
Absolute stereochemistry.

L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)



RN 786705-25-7 CAPLUS
CN 2-Pyrimidinamine, 4-[5-methyl-6-(4-piperidinyl)-3-[3-(trifluoromethyl)phenyl]-4-pyridazinyl]-N-[(1S)-1-phenylethyl]- (9CI) (CA INDEX NAME)

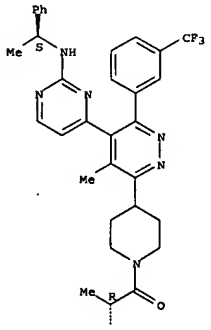
Absolute stereochemistry.



L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)
RN 786705-27-9 CAPLUS
CN Piperidine, 1-[(2R)-2-hydroxy-1-oxopropyl]-4-[4-methyl-5-[2-[[(1S)-1-phenylethyl]amino]-4-pyrimidinyl]-6-[3-(trifluoromethyl)phenyl]-3-pyridazinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A